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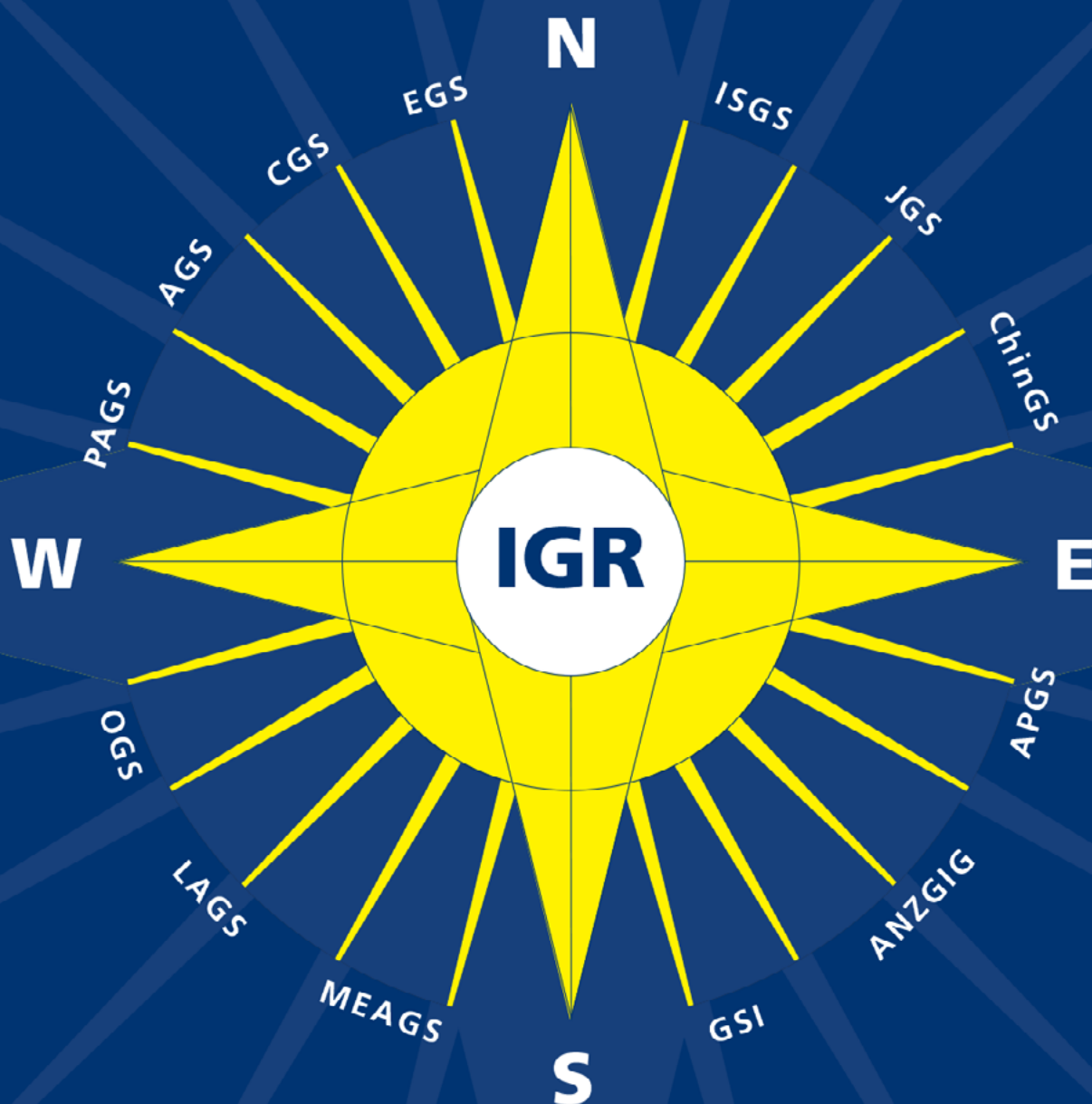
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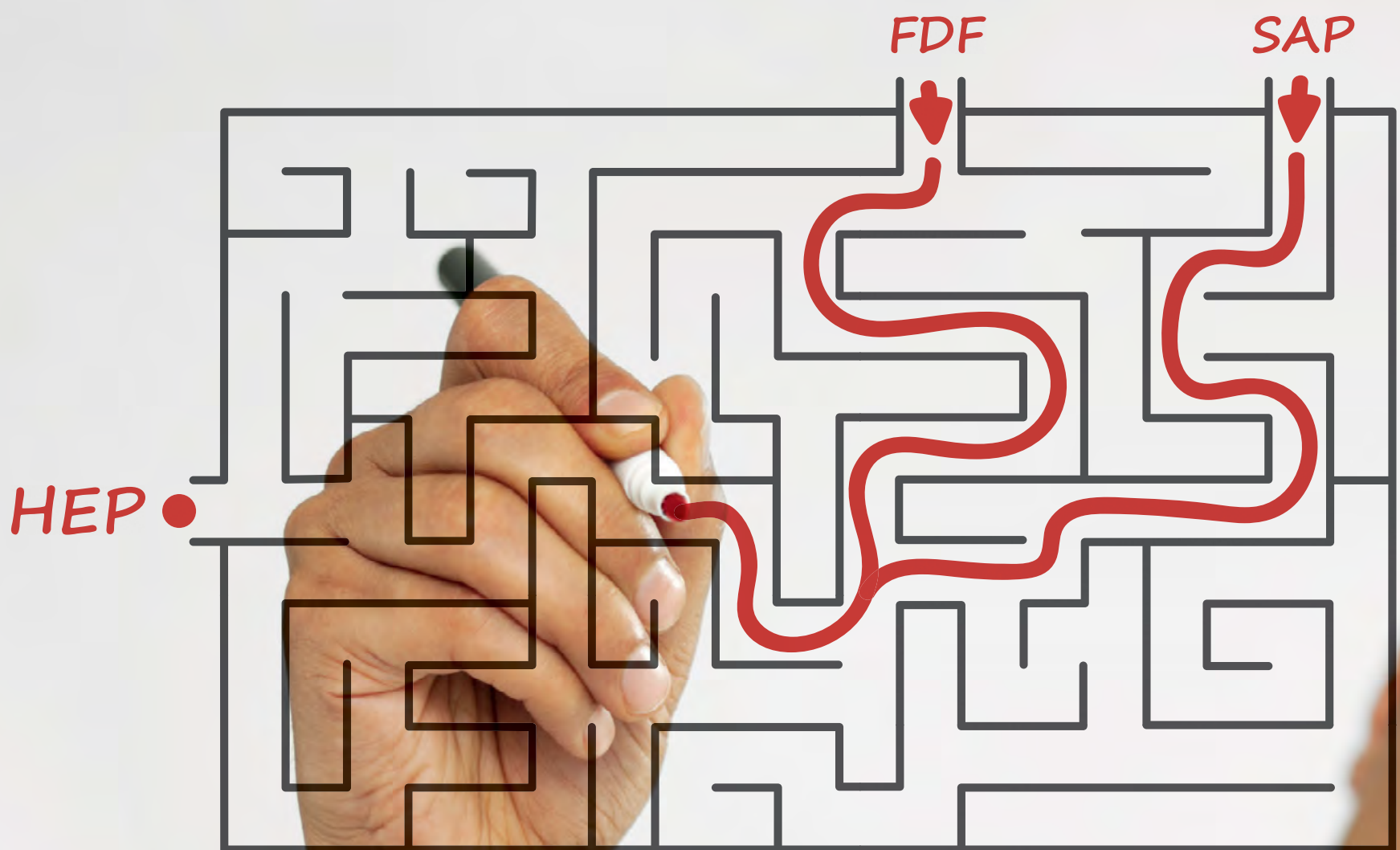
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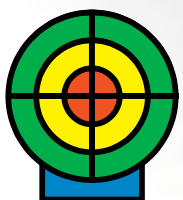
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Volume 17 no. 1



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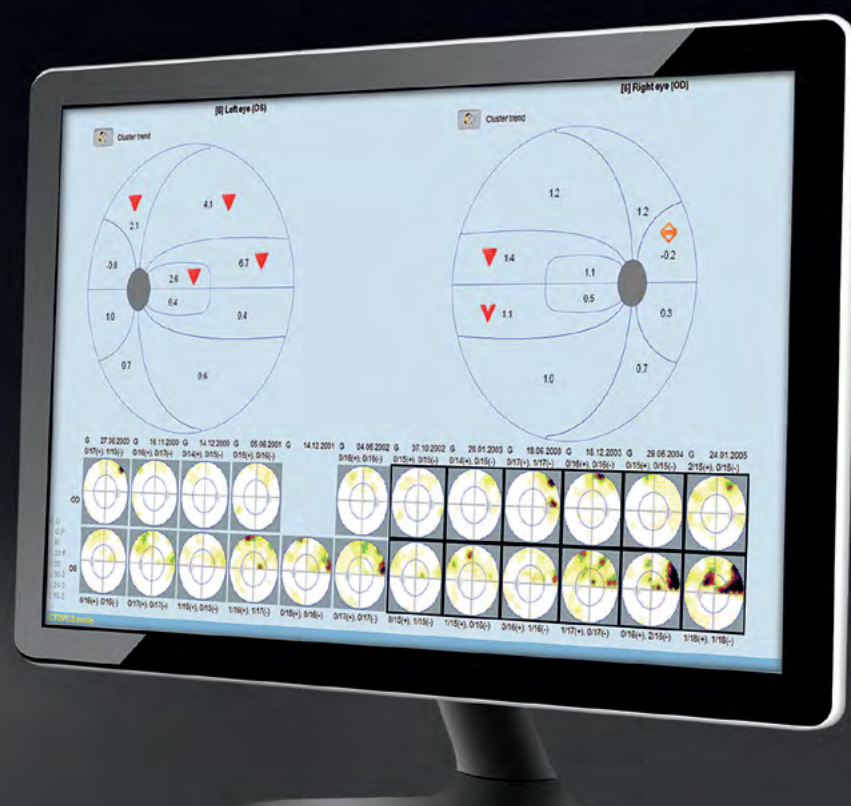
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WORLD GLAUCOMA WEEK 2016

March 6–12, 2016



www.worldglaucomaweek.org  

From the WGA Executive Office

The year 2016 has arrived and before saying a final goodbye to the previous year, we want to send out a special thanks to all individuals and WGA industry members who have supported us in making Volume 16 of ***International Glaucoma Review* successful** (see page 5 for a list of reviewers of this volume).

Over the past year, *International Glaucoma Review* has once again proven its value and IGR receives more readers every day via new applicants from Glaucoma Society Members. **Important steps were also taken during the past months to increase the visibility and outreach of IGR among healthcare professionals active the field of Ophthalmology in Africa.** Via the glaucoma network, suggestions and referrals were provided to expand our distribution channels in Africa.

And there are plenty more important initiatives ahead of us this year. Currently, numerous glaucoma specialist have agreed to participate in the upcoming **WGA 10th Consensus** on the **Diagnosis of Primary Open-Angle Glaucoma**. The results will be discussed on **April 30, 2016** in Seattle preceding ARVO (check www.worldglaucoma.org/consensus-10/ for the latest details). Key sections of this year's consensus meeting are: 1. Structure; 2. Function; 3. Structure/Function Relationship; 4. Risk Assessment (Ocular); 5. Risk Assessment (Systemic); and 6. Screening.

Reoccurring this year is the global awareness campaign '**World Glaucoma Week**'! From **March 6 through 12** many events are being held to focus attention on Glaucoma. If you are planning on organizing a special activity, do not forget to include it on our World Glaucoma Week world map (www.worldglaucomaweek.org)!

Please take a moment now to mark your agenda with the following important dates:

- World Glaucoma Week 2016: March 6–12, 2016
- 10th Consensus meeting 2016: April 30, 2016, Seattle, WA, USA
- 7th World Glaucoma Congress: June 28–July 2, 2017, Helsinki, Finland

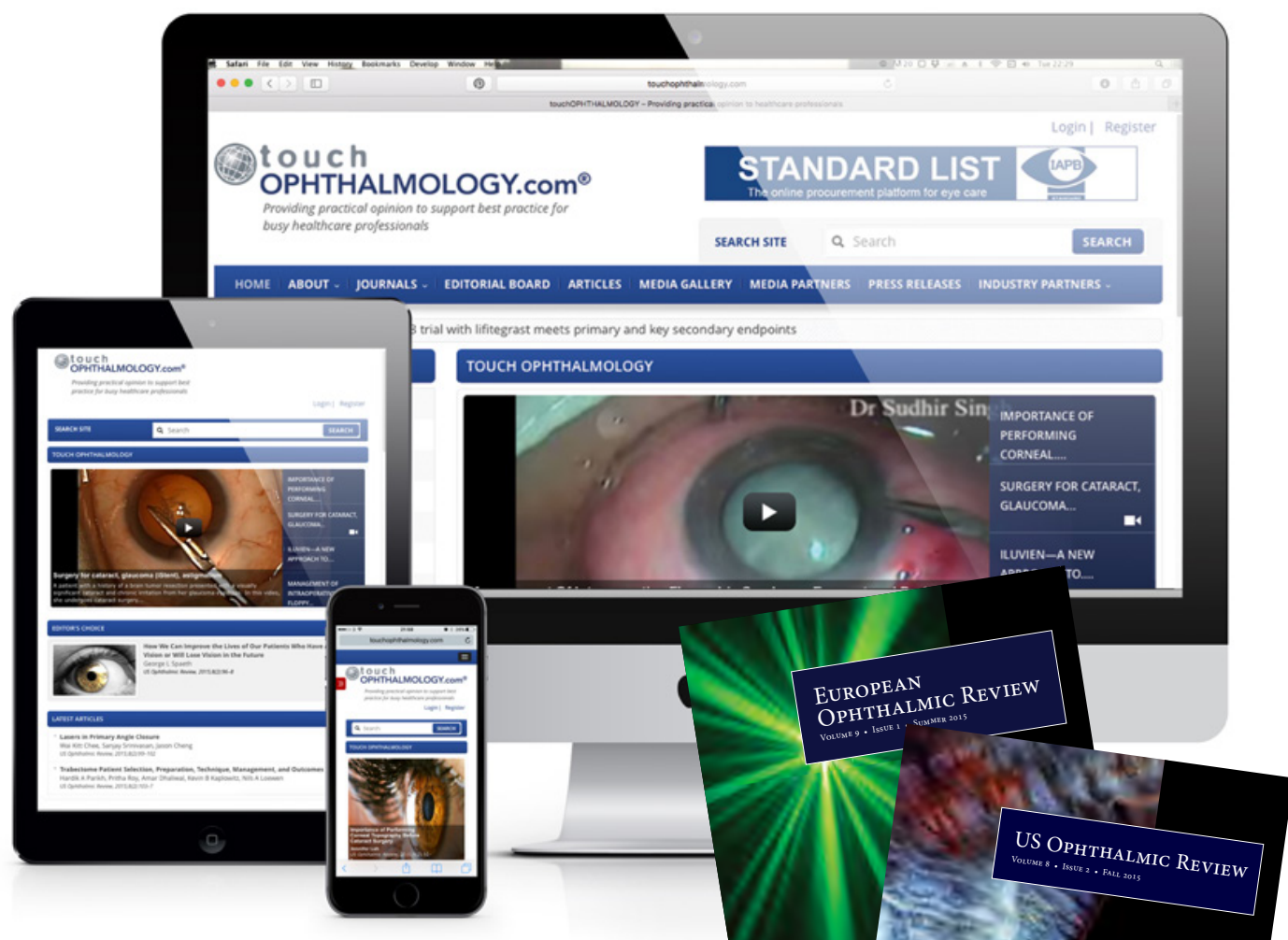
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Professor Dr. Robert D. Fechtner, Executive Vice President



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Evaluation of primary open-angle glaucoma clinical practice guidelines

Wu AM, Wu CM, Young BK, Wu DJ, Chen A, Margo CE, Greenberg PB

(abstract no. [61044](#))

Canadian Journal of Ophthalmology 2015; 50: 192-196

Towards axonal regeneration and neuroprotection in glaucoma: Rho kinase inhibitors as promising therapeutics

Van de Velde S, De Groef L, Stalmans I, Moons L, Van Hove I

(abstract no. [61357](#))

Progress in Neurobiology 2015; 131: 105-119

iStent with Phacoemulsification versus phacoemulsification alone for patients with glaucoma and cataract: A meta-analysis

Malvankar-Mehta MS, Iordanous Y, Chen YN, Wang WW, Patel SS, Costella J, Hutnik CM

(abstract no. [61607](#))

PLoS ONE 2015; 10: e0131770

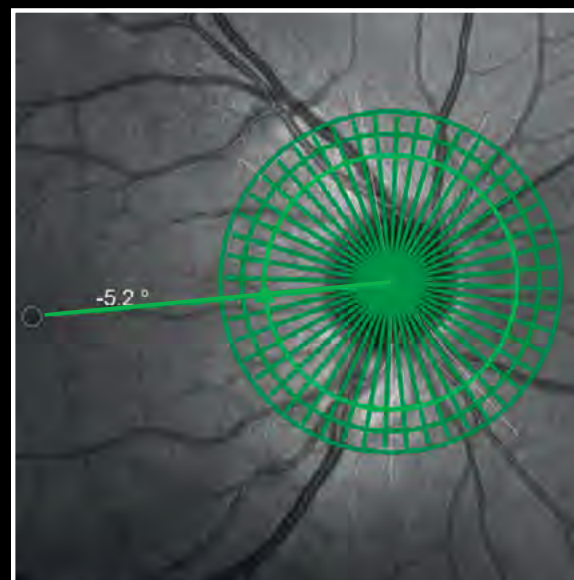
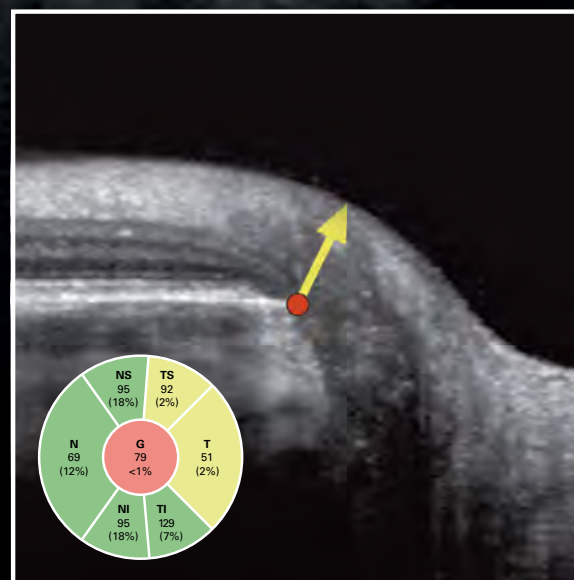
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Meeting Highlights

Top-Five of the Glaucoma Society of India Annual Meeting Mumbai, India, October 2–4, 2015



Prateep Vyas, Indore, India

Teaching and training for better Glaucoma services to the community

- In India, about 12 million people are estimated to have glaucoma which is a leading cause of irreversible blindness, accounting for about 13% of all blind people in the country. Epidemiological data suggest that more than 90% of glaucoma cases in India are undiagnosed. Causes of gross under-diagnosis include lack of awareness and education in the public and lack of glaucoma related health services to the community due to shortage of human resources among others. A sustained educational campaign is required to bridge this gap. A new model to educate the public as well as health care providers was discussed. The model is a win-win situation for all.

(S.S. Pandav)

- The importance of good clinical examination and documentation was highlighted and the fact that newer technology may add value to your clinical diagnosis was reiterated. However, there is no substitute patient centric approach in clinics. None of the technology at our disposal offers acceptable sensitivity and specificity and it is likely that based on just these reports either glaucoma can be over-diagnosed or missed. (G. Chandrasekhar)

The management of bleb failure

- Bleb failure management should actually begin by identifying and treating pre-operative risk factors, avoiding intra-operative risk factors and ultimately managing post-operative risk factors. The post-operative management depends on the timing of IOP rise and also the site of aqueous obstruction. It is not always that elevated IOP is the presenting feature of bleb failure.

(Sunil Jain)

ONH—how to differentiate between glaucoma and mimics of glaucoma

- The value of good clinical examination to differentiate between conditions that can be mistaken for glaucoma, such as congenital anomalies (coloboma, pit, tilted disc, large disc, etc.), neurological, traumatic neuropathy, etc. was emphasized. Also, the role of imaging technology and other perimetry in differentiating glaucoma from mimics of glaucoma was highlighted. If the ONH and RNFL are not appropriately examined and correlated, this may lead to a wrong diagnosis of glaucoma. (Prateep Vyas)

The optic disc in myopia; what does it say

- Myopic disc can be mistaken for glaucomatous disc; tilted myopic disc alfa and beta zone of myopic disc should be differentiated from glaucomatous changes. Study of the lamina cribrosa and other disc parameters by newer imaging modalities may be helpful in differentiating myopic disc from glaucomatous disc. (Vinay Nangia)

Top-Five of the Nordic Glaucoma Meeting

Malmö, Sweden, September 18–19, 2015



Gauti Jóhannesson, Malmö, Sweden and Miriam Kolko, Copenhagen, Denmark

Preliminary results from ‘The Bergen Angle Closure Study’

The presentation covered the preliminary results from ‘The Bergen Angle Closure Study’. The study is first of all to document the prevalence of primary angle-closure suspects (PACS), primary angle closure (PAC) and primary angle-closure glaucoma (PACG) in a population of western Norwegian descent (Caucasians). More than 4000 randomly selected persons older than 40 years of age will be screened, while those with narrow anterior chamber angles will undergo further investigations. So far, 1000 persons have been examined with a 60% response rate. Among them eight PACG, 12 PAC and 27 PACS have been identified. Even though the results are preliminary, the incidence of primary angle-closure glaucoma seems to be far more common than anticipated until now. (J. Askvik, Norway)

How can we improve glaucoma care?

The presentation highlighted the challenges of glaucoma care in Europe as summarized at the Closed Meeting of the European Glaucoma Society in June 2015. As many health systems are on the verge of insolvency, there is a need to find ways to do more with less money. As all impacts (good and bad) – including costs in health care – arise from decisions made by ophthalmologists, changes such as the following are needed: (1) Make strategic choices (provide citizens/patients with only the care they need, not trying to aim to serve everything to everybody); (2) Prioritize most resources to prevent permanent visual disability by segmenting the patients’ risk; (3) Produce high-volume, good-enough quality and low-cost services by standardizing ‘usual’ (non-urgent) care; and (4) Produce services efficiently, e.g., by implementing virtual clinics/telemedicine. In conclusion, ‘we cannot solve our problems with the same thinking we used when created them’ (Albert Einstein). Therefore, we need radical and significant changes in our thinking and behavior by starting with a belief that more is possible with less money. (A. Tuulonen, Finland)

Risks for glaucoma caused visual impairment

The presented study identified risk factors for glaucoma. Higher IOP and worse visual field status at baseline were important risk factors for glaucoma-induced visual impairment. Older age at death was another important risk factor for glaucoma blindness, a fact that might make it particularly relevant to include patient's life expectancy, when calculating the individual risk of blindness. Visual field defects near the point of fixation (often called 'threat to fixation') did not add any significant risk when the stage of visual field loss was taken into account. (D. Peters, Sweden)

Glaucoma-induced visual loss in Iceland

The presentation summarized the incidence of blindness caused by glaucoma in Iceland. In the 1950s, glaucoma caused more than half of all blindness in Iceland, which meant that at that time the country had a higher prevalence of glaucoma blindness than any other European country. As a result of increased awareness, preventive measures and new treatments, glaucoma now accounts for only 4% of blindness according to the Icelandic Organization of the Visually Impaired. (E. Gunnlaugsdóttir, Iceland)

Glaucoma-caused visual impairment in Finland 1983-2013/Prevalence, incidence, choice of treatment—a Danish nationwide study

The comprehensive population registers in Finland and Denmark were used to obtain data on the burden of glaucoma in each of the countries. Similar results were obtained in the independent registers. Hence, the number of patients treated for glaucoma was 83.675 (approx. 1.5% of the population) in Finland and 95.643 (approx. 1.7% of the population) in Denmark, numbers that are very similar. In both countries the number of patients treated for glaucoma has doubled since the 1990s. Based on the Finnish Registry of Visual Impairment (VI) the mean age of VI registration has deferred by 5,1 years during the past 30 years. Despite this favorable development, VI is estimated to increase due the increased number of glaucoma patients from 83.675 in 2012 to 120.000 in 2040. Eighty-plus-years-old glaucoma patients will increase by 135% in Finland. Overall, numbers from Finland and Denmark showed a similar pattern and future studies should compare registers in the Nordic countries. (H. Uusitalo, Finland and M. Kolko, Denmark)



Top-Five of the 31st Korean Glaucoma Society Annual Meeting Seoul, Republic of Korea, November 20–21, 2015



Joon Mo Kim, Seoul, Korea

Central visual field and macular ganglion cell/inner plexiform layer (GCIPL).

The 10-2 VF test points correlated significantly with GCIPL thickness in localized arcuate patterns mostly limited within the central 4.8.x 4.0 mm area. Correction for RGC displacement increased the correlation coefficient only for the innermost VF test locations. Given the overlapping nature of structure-function relationships, a smaller number of VF test locations may be used to summarize macular functional damage. (Ji-Woong Lee, Pusan, Korea)

Korean epidemiological results: Korea National Health and Nutrition Examination Survey (KNHANES).

Elevated IOP was correlated with obesity and metabolic syndrome. Myopia was related with high IOP and increased glaucoma prevalence. Disc hemorrhage incidence increased with age. Beta zone parapapillary atrophy and disc torsion were related with the location of RNFL defect. Superior segmental optic hypoplasia was associated with maternal history of diabetes and parental history of ischemic heart disease. (Joon Mo Kim, Seoul, Korea)

Optic nerve head (ONH) blood flow using indocyanine green angiography (ICGA).

The microvascular anatomy from the short posterior ciliary artery to the prelaminar tissue remains controversial. This study demonstrated that ONH filling was synchronized with the filling of the juxtapapillary choroid. In addition, microvessels between the parapapillary choroid and the ONH were identified. The finding suggests that prelaminar tissue is largely supplied by the small vessels arising from the choroid. (Tae-Woo Kim, Bundang, Korea)

Body posture and anterior chamber angle.

Little is known about the ACA dimension in lateral decubitus (LD) posture. The authors performed ACA imaging with anterior segment OCT with two posture conditions of sitting and left LD. The ACA parameters (TIA, AOD500, TISA 500) on the non-dependent (higher) side of fellow eyes in the LD posture were significantly reduced compared to those in the sitting position. (Ji-Hye Park, Seoul, Korea)

Effect of Bergmeister papilla on disc parameters in SD-OCT.

Bergmeister papilla is a remnant of the hyaloids artery fibrous sheath. Covering disc type and lifting edge type were the most common OCT findings. Its effects on SD-OCT parameters including optic nerve head parameters (small C/D ratio & cup volume), RNFL thickness, and measurement repeatability. Bergmeister papilla could be a pitfall in the interpretation of data, especially in glaucoma. (Jae Hoon Jeong, Seoul, Korea)

Top-Five of the Russian Glaucoma Society Congress

Moscow, Russia, December 4-5, 2015



by Eugeny Egorov, Moscow, Russia

The Russian Glaucoma Society (RGS) Congress, held in Moscow, assembled about 1200 participants. Within the sessions about 100 reports were presented by speakers from 15 countries.

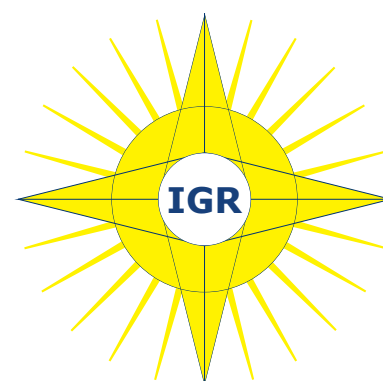
- Morphological characteristics of optic nerve head in glaucoma patients were highlighted in an honorary lecture by Prof. Vladimir Strakhov (Yaroslavl, Russia).
- Prof. Clement Vass (Vienna, Austria) shared his experience with the use of modern visualization technologies.
- The discussion about the indications for surgical treatment of congenital glaucoma was the keynote of the speech of Prof. Olga Kuleshova (Novosibirsk, Russia).
- Classification of glaucoma refractoriness and indications for reoperation were presented by the Vice-President of the RGS, Prof. Valeriy Elichev (Moscow, Russia).
- An attempt to create an optimal scientifically based system of management of diagnosis and treatment process in patients with primary open-angle glaucoma was made in the report of the young scientists group RGS – Scientific Vanguard (43 investigators from four CIS countries).



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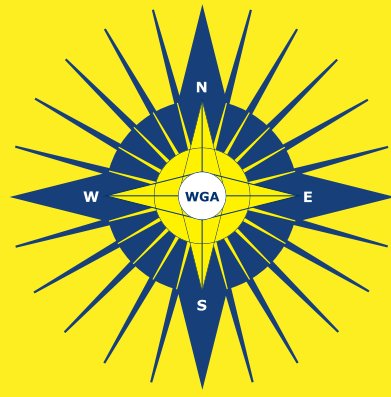
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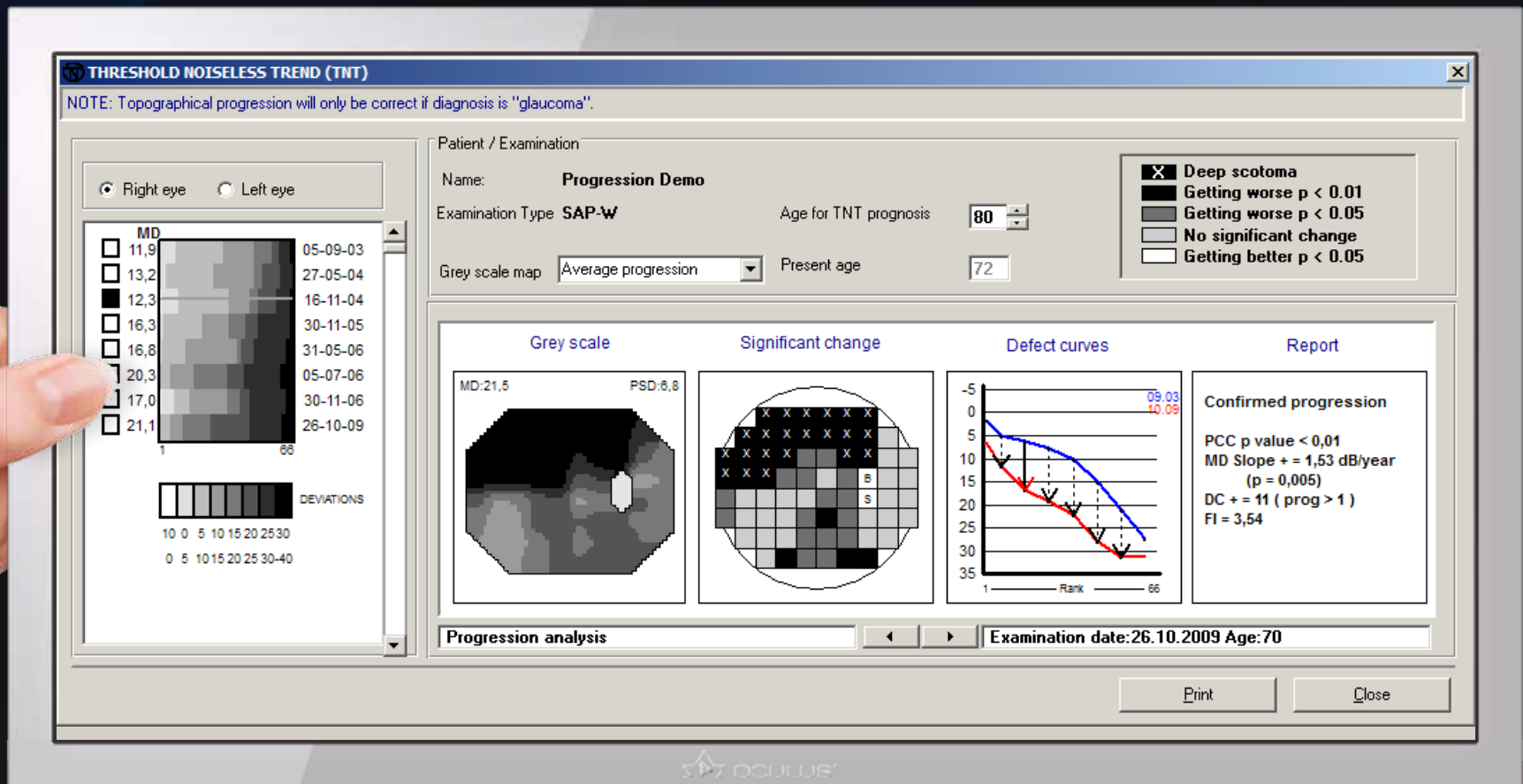
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Editor's Selection

With the multitude and variety of publications it seems almost impossible for the ophthalmologist to intelligently read all the relevant subspecialty literature. Even the dedicated glaucomatologist may have difficulty to absorb 1200+ yearly publications concerning his/her favorite subject. A solution to this confusing situation may be a critical selection and review of the world literature.



Robert N. Weinreb, Chief Editor

Quality of Life

Influence of Vision on Falls and Injuries



Comment by **Pradeep Ramulu**, Baltimore, MD, USA

61415 Investigating the Influence of visual function and systemic risk factors on falls and injurious falls in glaucoma using the structural equation modeling, Yuki K, Asaoka R, Tsubota K, PLoS ONE 2015; 10: e0129316

Glaucoma has previously been associated with higher rates of falls and fall-related injuries, with as many as 50% of patients having been noted to fall in a given year. Yuki *et al.* add to this literature by **retrospectively examining fall rates in 365 Japanese POAG patients**. They find a somewhat lower likelihood of falls in the prior year (15%), perhaps reflecting the relatively mild level of visual field damage (better and worse-eye MD of -2.7 and -6.4 dB in the fallers) and the retrospective design (in which some may not recollect their past falls).

Worse-eye visual acuity (VA) as the primary visual variable associated with falls

Unlike prior studies that have found visual field loss, particularly loss in the inferior field, to be a primary risk factor for falls, **the current study identified worse-eye visual acuity (VA) as the primary visual variable associated with falls**, though the difference in VA between fallers and fallers was very small (0.01 logMAR units).

No association was observed between either better or worse-eye MD and the likelihood of a fall in the last year – a surprising finding given that the falls literature has generally shown that visual field loss is more predictive of fall risk than VA. **This finding may again reflect the relatively early stage of disease in the study population, in which loss of acuity in one eye (and the depth perception deficits arising as a result) may be of greatest relevance.** Finally, it is notable that 40% of persons falling experienced an injury, highlighting the significant risk to health associated with falling, and the need to address falls in our patients at higher risk.

Anatomical Structures

Peripapillary Retinal Epithelium



Comment by **Tae-Woo Kim**, Bundang-gu, Seongnam, Korea

61562 Acute peripapillary retinal pigment epithelium changes associated with acute intra-ocular pressure elevation, Wang YX, Jiang R, Wang NL, Xu L, Jonas JB, Ophthalmology 2015;122(10):2022-2028

β -zone peripapillary atrophy (PPA) is known to be associated with glaucoma development and progression. The cause of the development and enlargement of β -zone in association with glaucoma remains to be elucidated. Wang *et al.* **assessed changes in the peripapillary RPE in association with acute IOP elevation provoked by a dark room prone provocative test (DRPPT)** in 45 eyes of 35 patients.

The findings of this study suggest the possibility that the development or enlargement of the parapapillary β -zone is influenced by a rise in IOP

They found that **18 out of the 19 eyes with an acute rise in IOP (> 15 mmHg) showed a folding and centrifugal sliding, or both, of the end the RPE layer on the peripapillary Bruch's membrane.** The RPE changes were located most often at the temporal pole of the ONH, followed by the nasal pole. The RPE changes were not detected at the inferior or superior disc poles. On the day after the DRPPT, the RPE end moved back to the end of peripapillary Bruch's membrane. None of the eyes who had IOP elevation less than 15 mmHg after the DRPPT showed RPE changes.

The findings of this study suggest the possibility that the development or enlargement of the parapapillary β -zone is influenced by a rise in IOP. Since the β -zone PPA is characterized by the absence of RPE, it may be conceived that long-standing IOP induces sustained centrifugal sliding of the RPE, and thereby development of β -zone PPA. However, further study is needed to confirm whether the study finding observed in this study on eyes with acute IOP elevation can substantially explain the development of β -zone PPA, which is a slowly occurring process over a long period. In addition, it is noteworthy that β -zone is also commonly found in glaucomatous eyes with IOP within the statistically normal limit.

RNFL in Parkinson's Disease



Comment by **Chris Leung**, Hong Kong, P.R. China

61397 Scanning laser polarimetry and spectral domain optical coherence tomography for the detection of retinal changes in Parkinson's disease, Stemplewitz B, Keserü M, Bittersohl D, Buhmann C, Skevas C, Richard G, Hassenstein A, Acta Ophthalmologica 2015; Jun 10. [Epub ahead of print]

Findings from studies investigating retinal changes measured by optical coherence tomography (OCT) in Parkinson's disease have been inconsistent. Stemplewitz and colleagues revisited the issue and examined **retinal nerve fiber layer (RNFL) and macular thickness measurements obtained with spectral-domain OCT (Cirrus HD-OCT) and scanning laser polarimetry (SLP) (GDx VCC) in patients with Parkinson's disease and healthy controls**. While no significant differences in average/quadrant RNFL thicknesses measured by OCT were found between the groups, **the average/inferior RNFL thicknesses and NFI (nerve fiber index) measured by SLP were smaller in patients with Parkinson's disease**. SLP measures RNFL birefringence/retardance values around the optic disc and converts these values into RNFL thicknesses using a fixed conversion factor. Although the discrepancies in findings between OCT and SLP could be explained by the fact that reduction in RNFL retardance may occur before RNFL thinning (which has been demonstrated in animal models of optic nerve injury – Fortune B, et al. Invest Ophthalmol Vis Sci 2008;49:4444-4452; Fortune B, et al. Invest Ophthalmol Vis Sci 2013;54:5653-5661), it is worth noting that the difference in the SLP average RNFL thickness between the patients and controls were minute ($57.1 \pm 0.3\mu\text{m}$ versus $55.8 \pm 0.5\mu\text{m}$, $p = 0.04$). Further, **patients with Parkinson's disease were significantly older (64.3 ± 12.3 years versus 56.9 ± 13.0 years). Age-related RNFL loss would complicate the interpretation of RNFL measurements**. Investigating the rate of change of RNFL thickness in longitudinal studies would be a more informative approach to address whether the RNFL may serve as a biomarker for neurodegenerative diseases.

Basic Science

Effects of Steroids on the Trabeculum



Comment by **Abbot Clark**, Fort Worth, TX, USA

61276 Dexamethasone stiffens trabecular meshwork, trabecular meshwork cells, and matrix, Raghunathan VK, Morgan JT, Park SA, Weber D, Phinney BS, Murphy CJ, Russell P, Investigative Ophthalmology and Visual Science 2015;56:4447-4459

Glucocorticoid (GC)-induced ocular hypertension (OHT) is an important side effect of prolonged GC treatment, which can lead to iatrogenic open-angle glaucoma that clinically is very similar to primary open-angle glaucoma. GCs induce a wide variety of changes in the trabecular meshwork (TM), but the molecular mechanisms responsible for GC-OHT are still unknown. A recent report by Raghunathan and colleagues has nicely shown that treatment with the potent GC dexamethasone stiffens TM cells and tissues, which they suggest contributes to GC-OHT. **Treatment of cultured human TM cells with dexamethasone caused a significant increase in TM cell stiffness measured by atomic force microscopy (AFM).** The authors removed the TM cells and used AFM to demonstrate that the extracellular matrix (ECM) of dexamethasone treated TM cells was also significantly stiffer compared to the ECM of control TM cells. Proteomic examination of this ECM showed increased expression of glaucoma-associated proteins including myocilin, decorin, fibrillin, and secreted frizzled related protein (SFRP1). SFRP1 is an antagonist of the Wnt signaling pathway, and previous studies have reported elevated SFRP1 in glaucomatous TM cells and tissues. Increased SFRP1 expression elevated IOP in perfusion cultured anterior segments as well as in mouse eyes. This suggests that there may be cross-talk between the GC and Wnt signaling pathways in the TM. Raghunathan and colleagues also treated rabbits with topical ocular 0.1% dexamethasone eye drops for three weeks, and showed that the dexamethasone treated TM tissues were also significantly stiffer compared to the TM of untreated eyes. **The authors conclude that the GC mediated changes in biophysical properties of TM cells, tissues, and ECM (i.e., increased stiffness) are associated with increased aqueous outflow resistance and elevated IOP.** Although these are important and significant findings, there is no direct evidence that these changes are responsible for GC-mediated changes in aqueous outflow resistance and elevated IOP. The rabbits in this study did not develop elevated IOP, and the GC responder status of the human TM cells used in these studies likely was unknown.

Neuronal Function in Experimental Glaucoma



Comment by **Koen Vermeer**, Rotterdam, The Netherlands

60996 Relating retinal ganglion cell function and retinal nerve fiber layer (RNFL) retardance to progressive loss of RNFL thickness and optic nerve axons in experimental glaucoma, Fortune B, Cull G, Reynaud J, Wang L, Burgoyne CF, Investigative Ophthalmology and Visual Science 2015;56:3936-3944

The nature of the relation between retinal function and structure is a topic that is notoriously difficult to study in a clinical setting. Despite impressive improvements in imaging technology in recent years, clinically used measures such as thickness and retardance of the RNFL are still surrogate markers for actual loss of axons.

Fortune *et al.* studied **changes in function and structure in experimental glaucoma (EG) in 39 nonhuman primates (NHPs)**. They considered RNFL thickness (by SD-OCT) and retardance (by scanning laser polarimetry; SLP) as *in-vivo* structural parameters, mfERG as *in-vivo* functional parameters and complete postmortem optic nerve axon counts as *ex-vivo* structural parameters.

Analysis of the in-vivo data by linear regression showed that retardance was significantly affected before a change in RNFL thickness was measured.

Retardance was significantly affected before a change in RNFL thickness was measured

Similar results were found for the mfERG high-frequency component (HFC) amplitude.

These results indicate that both structural and functional changes occur before loss of RNFL tissue can be demonstrated by thickness measurements.

Relative axon counts (ratio of axon counts in the EG eye over the control eye) were obtained in 31 NHPs. Linear regression with RNFL thickness showed no significant offset, suggesting that RNFL thickness loss was a good surrogate for loss of axons in these eyes. Linear regression with the other parameters again showed significant loss of RNFL retardance and mfERG HFC amplitude before differences in optic nerve axon counts could be demonstrated.

Structural and functional changes occur before loss of RNFL tissue can be demonstrated by thickness measurements

In conclusion, loss of both retinal ganglion cell function and RNFL retardance was demonstrated in this study before loss of RNFL thickness and optic nerve axons. This suggests that clinical care could benefit from considering changes within the RNFL itself, such as retardance (measured by

SLP or polarization-sensitive OCT¹) or OCT-derived attenuation coefficients.² While these results obtained in EG in NHPs may not be directly transferable to the natural history of glaucoma in human eyes, they provide a great foundation for the design of new clinical studies addressing structure-function relationships.

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RGC Regeneration



Comment by **Franz Grus**, Mainz, Germany

61071 Influence of extracellular matrix components on the expression of integrins and regeneration of adult retinal ganglion cells, Vecino E, Heller JP, Veiga-Crespo P, Martin KR, Fawcett JW, *PLoS ONE* 2015; 10: e0125250

Apoptotic processes are thought to play a major role in the death of retinal ganglion cells (RGC) in glaucoma patients. However, it is still unclear which factors determine if some RGCs are resistant to injury at some extent and others are not. RGCs do not respond in the same way to damage and the capacity of RGCs to survive or regenerate is variable. Elena Vecino *et al.* analyzed in this important paper the extracellular matrix (ECM) and integrin expressions. The authors used different ECM substrates such as Poly-L-Lysine (PL), PL plus laminin (L), collagen I (CI), collagen IV (CIV), or fibronectin (F) to test their effects on the survival rate of primary RGC cultures. Additionally, they looked for the integrin expression after ten days and if the different substrates had any effect on the length and branching complexity of the neurites of the RGCs.

The authors could demonstrate that PL and L were associated with the greatest survival rate of RGCs. Furthermore, they could clearly show that the substrates affected the number and lengths of the RGC neurites. L led to the stimulation of the longest outgrowth. Interestingly, the authors could find at least three different types of RGCs in terms of their capacity to regenerate and the growth of neurites.

This is an extremely interesting and important result, because there is still no explanation for the difference of RGCs in their sensitivity to damage. This paper provides really interesting hints to different type of characteristics of RGCs. I would encourage the authors to continue this

interesting work and further characterize the RGC subtypes they demonstrated in their paper on the molecular level, *e.g.*, by proteomics techniques. Those molecular markers might then help to understand the differences between the subtypes and the possible pathways involved.

Neuroprotective Effects of Glucose



Comment by **Derek Welsbie**, Baltimore, MD, USA

61531 Effect of subconjunctival glucose on retinal ganglion cell survival in experimental retinal ischaemia and contrast sensitivity in human glaucoma, Shibeeb O, Chidlow G, Han G, Wood JP, Casson RJ, *Clinical and Experimental Ophthalmology* 2015;

Robert Casson and his colleagues in Adelaide have a series of papers showing that increasing intraocular glucose decreases retinal ganglion cell (RGC) death in rodent models of optic neuropathy, including glaucoma.¹⁻³ Moreover, they have some evidence to suggest that elevated glucose levels might actually improve the function of injured, but not yet dead, human RGCs, a concept known as neurorecovery.⁴ In this most recent study from his group, Shibeeb *et al.* test whether similar neuroprotection and neurorecovery could be achieved with subconjunctival administration of a highly-concentrated glucose solution. In the first part, **rats were given a large subconjunctival bolus of 50% glucose, enough to elevate the vitreous levels of glucose nearly two-fold**. One hour after the challenge, severe ocular hypoxia was produced, an injury well-known to trigger RGC cell death. In this model, known as ischemia/reperfusion, the rat anterior chamber was cannulated and the intraocular pressure raised well above the systolic blood pressure for one hour, totally occluding blood flow. One week later, the number of surviving RGCs in the retina was measured using conventional RGC markers and by counting optic nerve axons. As expected, control-treated eyes demonstrated the RGC loss typical of the model. In contrast, **eyes pretreated with subconjunctival glucose had only half the RGC death** (although there was significant variability). While exciting, it remains to be seen whether the protection is sustained (beyond one week), whether a similar effect would be seen in the setting of a treatment paradigm (as opposed to prevention) and whether the rescued RGCs remain functional, all hallmarks of a successful neuroprotective strategy.

In the second part, using a cross-over design, Shibeeb and coauthors identified five **pseudophakic primary open-angle glaucoma patients and randomized them to receive subconjunctival glucose or an osmolarity-matched saline control**. Of note, the injection was accompanied by marked pain, precluding the authors from considering similar formulations in the future. Before and two hours after treatment, contrast sensitivity was measured over a range of spatial frequencies. Consistent with their previous work, the authors found that **glucose-treated eyes actually had improved contrast sensitivity**. However, before concluding that glucose

is promoting neurorecovery, it will be important to show that the RGC is the cellular substrate of the effect as many other cells and structures could be affected by the sudden increase in glucose. Nonetheless, this paper builds upon a body of work which has repeatedly shown that elevated glucose levels influence the RGC response to hypoxic injury, through a mechanism that is surely the goal of current research.

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Clinical Examination Methods

24-h IOP Monitoring



Comment by **Tony Realini**, Morgantown, WV, USA

61162 Efficacy of a contact lens sensor for monitoring 24-h intraocular pressure related patterns, Mansouri K, Weinreb RN, Liu JH, PLoS ONE 2015; 10: e0125530

Mansouri and colleagues recently reported the results of a prospective study in which 33 subjects (31 healthy and two with primary open-angle glaucoma) underwent observation during a 24-hour period while wearing a Triggerfish contact lens sensor in one randomly selected eye and undergoing every-two-hour pneumatonometry in the fellow eye with the specific goal of validating the Triggerfish system's ability to detect changes in intraocular pressure (IOP) known to occur during the wake to sleep transition and its ability to infer heart rate based on ocular pulse frequency. The investigators' larger goal was to demonstrate that the Triggerfish device can identify known physiologic IOP behavior, and thus can be useful in assessing IOP in the clinical setting of glaucoma care.

The clinical significance is that this device can be used to infer the nature of IOP behavior outside office hours, including the critical time during sleep when IOP is highest

The device has already been shown to detect large acute changes in IOP associated with blinks and saccades. **The current study demonstrates the ability of Triggerfish to detect small changes in IOP that may be more relevant to the magnitude of IOP changes that we might be interested in during clinical 24-hour IOP monitoring.** These data, in combination with other published studies, demonstrate that the Triggerfish device can provide relevant information regarding IOP behavior. The clinical significance is that this device can be used to infer the nature of IOP behavior outside office hours, including the critical time during sleep when IOP is highest. Further, as the importance of ocular perfusion pressure (OPP) – particularly nocturnal OPP – continues to become apparent in glaucoma, this device provides the means of collecting 24-hour IOP data which, when paired with 24-hour ambulatory blood pressure monitoring, can provide a valid representation of circadian OPP without the need for overnight evaluation in a clinical research facility. The epidemiologic importance of OPP and glaucoma prevalence has been well established in cross-sectional studies. **Coupling Triggerfish with ambulatory blood pressure monitoring provides a mechanism for conducting longitudinal studies evaluating the relationship between OPP and glaucoma progression risk.**



Comment by **Syril Dorairaj**, Jacksonville, FL, USA and **Marcos Pereira Vianello**, Belo Horizonte, Brazil

61386 Estimation of 24-hour intraocular pressure peak timing and variation using a contact lens sensor, Liu JH, Mansouri K, Weinreb RN, PLoS ONE 2015; 10: e0129529

The search for a continuous intraocular pressure (IOP) monitoring device to replace Goldmann applanation tonometer (GAT) remains a holy grail in ophthalmology. As the only modifiable parameter for treating glaucoma, a precise and continuous measurement of IOP is imperative. A perfect continuous monitoring device would be comfortable, easy to use in office and outside in home settings, noninvasive, economical, accurate, reproducible and should be in mmHg for comparison.

Although some studies have pointed that 24-hour rhythm is unaffected by nocturnal awakening in healthy individuals, it is certainly uncomfortable, anti-physiological and expensive to evaluate IOP changes in sleep lab settings. Recently, a wireless contact lens sensor (CLS) for 24-hour IOP monitoring was developed. It provides continuous monitoring of IOP, with good tolerability.

In the present study, Liu and colleagues compared **the 24-hour IOP monitoring curve in 30 healthy volunteers. The pneumatonometer was used in one eye and the contralateral eye was fitted with a CLS that monitored circumferential curvature in the corneoscleral region related to the change of IOP.** Although there is no algorithm that connects the CLS signals (in minivolts) to IOP values (in mmHg), the study tried to verify the correlation between estimates of IOP peak timing and IOP variations obtained by the two methods. The authors based their study on the principle that in healthy adults, 24-hour IOP rhythms in paired eyes are relatively symmetrical.

The authors tried to answer two questions in the study. Firstly, is the simulated peak timing based on 24-hour CLS data close to the 24-hour pneumatonometer peak timing? Secondly, do the simulated variations of the CLS 24-hour data correlate with the 24-hour variations of IOP data of the paired eye?

Both groups detected the mean peak timing outside office hours, during the sleep period. **The results pointed out that the 24-hour CLS data showed simulated peak timing close to the 24-hour IOP peak timing obtained using the pneumatonometer. However, the CLS output signal amplitude did not correlate with the amplitude of pneumatonometer IOP in the contralateral eye,** confirming the difficulty to establish a conversion formula from the CLS mV data to mmHg.

Advances in CLS technology in continuous monitoring of IOP has potential for changing the diagnosis and management of glaucoma. Contact lens sensor provides a good estimation of the habitual IOP peak timing but at this time further clinical trials are needed to demonstrate its validity in evaluating IOP variation.

Clinical Examination Methods

24-h IOP Monitoring and Chronic Hemodialysis



Comment by **Kaweh Mansouri**, Geneva, Switzerland

61584 Twenty-four-hour intraocular pressure monitoring in normotensive patients undergoing chronic hemodialysis, Panagiotou ES, Liakopoulos V, Giannopoulos T, Voudouragkaki IC, Demirtzi P, Paschalinou E, Nikitidou O, Kapis PV, Konstas AG, European Journal of Ophthalmology 2015;26(1):24-29

The effect of hemodialysis on intraocular pressure (IOP) has not been well-studied and remains controversial. Studies have found both an increase as well as decrease of IOP during hemodialysis. The low sampling rate of current tonometry techniques and the resultant high variability of IOP data are likely contributors to this confusion.

Panagiotou *et al.* investigated 24-h IOP characteristics of 18 non-glaucomatous subjects before and during hemodialysis. They obtained seven daily measurements (including two during the nocturnal period) using applanation tonometry in the habitual body positions. **They found statistically significantly higher mean IOP (+1.3 mmHg), peak IOP, and IOP fluctuations on the day of hemodialysis** compared to treatment-free day. These differences, however, were explained by a single time-point IOP difference (at 17.00, peak IOP) between the two treatment days. Overall, the IOP patterns were similar. Is that difference of any clinical relevance?

At present, it is unknown whether patients undergoing hemodialysis are at higher risk of glaucoma

Important limitations are the small sample size and the dependency of the significance of IOP findings on a single time-point IOP. In fact, although the time of peak IOP on treatment day corresponded with the end of the hemodialysis treatment, peak IOP also occurred at the same timepoint on the non-treatment day. This is surprising since studies show circadian IOP to be usually at its lowest in the late afternoon. It can be speculated that non-physiological (e.g., hemodialysis) or study-related factors may have contributed to this finding. The authors, however, did not find a correlation between IOP change and the duration of hemodialysis.

At present, it is unknown whether patients undergoing hemodialysis are at higher risk of glaucoma. Despite major shortcomings, this study has highlighted an interesting area of research.

Factors Affecting IOP



Comment by **Yvonne Buys**, Toronto, Canada

61532 Effect of different head positions in lateral decubitus posture on intraocular pressure in treated patients with open-angle glaucoma, Lee TE, Yoo C, Lin S, Kim YY, American Journal of Ophthalmology 2015;160(5):929-936

The literature regarding the influence of posture on intraocular pressure (IOP) has taught us that **as the head assumes a more dependent position IOP increases**. This study by Lee *et al.* confirms this finding in a group of 20 open-angle glaucoma subjects controlled with latanoprost. What is new, however, is exploring the effect of head position while in a common sleep position, lateral decubitus. IOP was measured in a random order with subjects in the right and left lateral decubitus position while varying the position of the head with respect to the thoracic spine; head 30 degrees higher, parallel and 30 degrees lower by stacking pillows.

It is time to think beyond the effects of position on IOP in isolation and start to consider the interaction of IOP, CSFp and BP

As expected, in the lateral decubitus position IOP was higher in the dependent eye and while in the lateral decubitus position IOP was higher when the head was 30 degrees lower. Although the magnitude of this effect varied by subject, in 50% it was ≥ 4 mmHg in the dependent eye with the head lowered compared to sitting reaching a maximum of 8.8 mmHg in one subject. **In contrast to other reports, this study failed to find a difference when comparing the better-to-worse eye** defining severity by either visual field mean deviation or pattern standard deviation. The authors **conclude by suggesting side sleepers consider elevating their head** to minimize this IOP increase, however, even with the head 30 degrees elevated, IOP was still higher in the dependent compared to the nondependent eye suggesting that perhaps a better recommendation would be to sleep supine with the head elevated.

The authors acknowledge some of the **limitations of their study including small sample size, laboratory setting which may not reflect what occurs during sleep and the short (five minutes) duration of the maintaining the position prior to measuring**. Larger questions, however, remain unanswered, namely what is the mechanism of posture-induced IOP changes, what is the effect of neck flexion on venous compression, what is the effect of position on cerebral spinal fluid pressure (CSFp) and blood pressure (BP), and can changing sleep position influence glaucoma progression rates. It is time to think beyond the effects of position on IOP in isolation and start to consider the interaction of IOP, CSFp and BP.

Rnfl and Retinal Venous Pulsations



Comment by **William Morgan**, Perth, Australia

61426 Correlation of retinal nerve fibre layer thickness and spontaneous retinal venous pulsations in glaucoma and normal controls, Golzan SM, Morgan WH, Georgevsky D, Graham SL, PLoS ONE 2015; 10: e0128433

The study of retinal venous pulsation and its association with glaucoma is attracting increasing interest because of the strong association between absent venous pulsation, the severity of glaucoma and its proclivity to progression. This paper offers a novel technique for measuring retinal venous pulsation. Typically, 50% of glaucoma subjects have spontaneous venous pulsation, which means that threshold measurements like venous pulsation pressure using ophthalmodynamometry can only be taken in half the glaucoma population and in a lesser proportion of the normal population. This newer technique uses high-quality video footage of the retinal vessels and automated image analysis algorithms to measure retinal venous transverse diameter, frame by frame and thereby calculate a pulsation amplitude in microns. Hence, a measurement can be derived for all patients and across different regions of vessels. This paper describes the **association between reduced venous pulsation amplitude and the presence and severity of glaucoma**. It discusses in some detail the potential reasons why this phenomenon occurs. One plausible reason is simply that there is reduced blood flow in regions where there is less nerve fiber layer (NFL) tissue due to reduced demand, and perhaps this is associated directly with reduced pulsation amplitudes. Interestingly, the y-intercepts (NFL) in the relation between pulsation amplitude and NFL thickness appear to be lower in the glaucoma group compared to the normal group, hinting that this in fact may not be the case.

Alterations in venous pulsation amplitudes occurring in glaucoma are not simply due to reduction in tissue requirement induced blood flow

This paper describes a measurement technique, which is potentially applicable to all subjects. It hints at the possibility that alterations in venous pulsation amplitudes occurring in glaucoma are not simply due to reduction in tissue requirement induced blood flow.

Glaucoma Detection by OCT



Comment by **Don Budenz**, Chapel Hill, NC USA

61553 Estimating lead time gained by optical coherence tomography in detecting glaucoma before development of visual field defects, Kuang TM, Zhang C, Zangwill LM, Weinreb RN, Medeiros FA, Ophthalmology 2015;122(10):2002-2009

Kuang *et al.* analyzed data of 75 glaucoma suspects who ultimately converted to glaucoma by visual field criteria and 75 normal subjects collected longitudinally as part of the Diagnostic Innovations in Glaucoma Study. Subjects had undergone time domain and then spectral domain OCT as part of the study as well as standard automated perimetry. **The investigators found that the glaucoma suspects had thinner average retinal nerve fiber layer (RNFL) thickness up to eight years prior to the development of visual field defects.** These findings are consistent with histology studies showing that there is a loss of nerve fibers that precedes detectable visual field loss as currently measured.

Glaucoma suspects had thinner average retinal nerve fiber layer (RNFL) thickness up to eight years prior to the development of visual field defects

It is important to clarify, as the authors also do, that **we are not to conclude that all glaucoma suspects showed thinning of the RNFL eight years prior to conversion to glaucoma** but that there were detectable differences between the two groups years in advance of conversion. The importance of this study is that the clinician can expect to see RNFL changes before visual field changes in glaucoma suspects over time. An **incorrect conclusion of these results would be to treat glaucoma suspects with normal visual field tests just because they have an abnormal RNFL.** Because there are many false positives in OCT testing, this practice would result in over-treatment. However, if the clinician sees thinning of the RNFL that is outside the normal thinning expected with aging, this should be considered evidence of glaucomatous change barring any non-glaucomatous conditions that could cause thinning of the RNFL. The study numbers are small between four to eight years but these studies are difficult to perform and the authors are to be commended for collecting longitudinal data of such high quality and the analysis of the data is sound.

OCT-Angiography



Comment by **Alon Harris**, Indianapolis, IN, USA

61541 Optical coherence tomography angiography of the peripapillary retina in glaucoma, Liu L, Jia Y, Takusagawa HL, Pechauer AD, Edmunds B, Lombardi L, Davis E, Morrison JC, Huang D, JAMA Ophthalmology 2015;133(9):1045-1052

Advancements in our ability to accurately quantify ocular blood flow and vascular health in ocular pathology hold great promise towards enhanced disease diagnosis and patient management. The **present study seeks to utilize OCT methodologies for linking peripapillary retinal perfusion and localized vascular density to distinguish glaucoma status and alignment with visual field damage.** This has been proposed previously as important,¹ as regional differences in blood flow alone were inconclusive, but when considered in proportion to the tissue bed being perfused, metabolic vulnerability was apparent. The authors' work is encouraging, as development of a technology capable of quantifying vascular density whilst simultaneously calculating the volume of perfused tissue promises new insights into the role of hemodynamics in the pathogenesis and progression of glaucoma. Specifically in the present study, **peripapillary flow and vessel density were significantly lower in glaucomatous eyes than in normal eyes and were highly correlated with visual field PSD in glaucomatous eyes.** The use of age-matched eyes between healthy and glaucomatous subjects is one strength of the current approach, as are the high repeatability and reproducibility numbers for the techniques implemented. **An obvious limitation is the small sample of 12 eyes per comparative group, as is the presence of potentially vasoactive medication use by subjects.** It also remains unclear if the selected areas for analysis represent the tissue most important in the disease process in terms of order of mechanistic vascular involvement. Important next steps should include a longitudinal study tracking and pacing the progression of changes in the described peripapillary flow and vessel density in relation to glaucomatous visual function and ocular tissue changes, to better describe the modalities' ability to describe structure/function/hemodynamics relationships and evaluate their ability to predict risk for the progression of glaucoma.

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Clinical Forms of Glaucoma

NTG Progression to Blindness



Comment by **Ki Ho Park**, Seoul, Korea

61017 Progression to legal blindness in patients with normal-tension glaucoma: hospital-based study, Sawada A, Rivera JA, Takagi D, Nishida T, Yamamoto T, Investigative Ophthalmology and Visual Science 2015;56:3635-3641

The authors evaluated the probability of normal tension glaucoma (NTG) progressing to legal blindness under standard ophthalmic care after a retrospective analysis of 382 NTG patients with a mean follow-up period of 13 years. Upon final examination, 34 patients had progressed to unilateral blindness and five to bilateral blindness. **Thus, the probability of patients with NTG progressing to unilateral blindness was 5.8% at ten years and 9.9% at 20 years;** that for bilateral blindness was 0.3% at ten years and 1.4% at 20 years. A lower initial best-corrected visual acuity (BCVA), a worse AGIS score, and the frequency of glaucoma-medication change during the follow-up period were significantly correlated with the development of blindness in at least one eye. The frequency of glaucoma-medication change might not be a cause of blindness but seems, rather, to be an epiphenomenon related to the medications prescribed during the disease-worsening period.

Special care should be taken to follow-up on NTG patients, especially those with worse best-corrected visual acuity and more advanced visual field loss at diagnosis

As for the study's strengths, a large number of NTG patients from one institute were followed-up on over a long duration. Also, the study provides an important reference even though the probability of blindness in eyes with NTG is much lower than previously reported in patients with high-tension glaucoma.

The major limitation of this study is the large proportion of patients lost during the initial follow-up period. This seems an important but inevitable issue in a study performed retrospectively. Another issue, not mentioned in the paper, was the lack of information on the degree of cataract, which could have affected visual acuity and the probability of blindness as well.

These issues notwithstanding, the study offers a clinically important message, which is that doctors should exercise caution with respect to their NTG prognoses when the patient shows low BCVA and advanced visual field loss at diagnosis.

Provocative Tests in PACG



Comment by **Min Hee Suh**, Busan, Korea

60890 Optic nerve head changes after short-term intraocular pressure elevation in acute primary angle-closure suspects, Jiang R, Xu L, Liu X, Chen JD, Jonas JB, Wang YX, *Ophthalmology* 2015;122:730-737

Jiang *et al.* investigated changes of the optic nerve head (ONH) morphology after acute IOP elevation during dark room prone provocative test (DRPPT) in acute primary angle-closure suspects. **Deepening and widening of the optic cup, decrease in neuroretinal rim width, and thinning of the lamina cribrosa (LC) was observed after darkness-induced acute IOP increase > 15 mmHg. Meanwhile, the diameter of the Bruch's membrane opening (BMO) and position of the anterior LC remained unchanged.** These results are in line with the study by Agumi *et al.* reporting the compression of prelaminar tissue without displacement of the anterior LC after acute IOP elevation in both glaucoma patients and healthy subjects.¹ Despite several limitations the authors mentioned in the discussion, this study has a strength in the study design. They enabled physiologic IOP elevation with relatively long duration by undergoing DRPPT for two hours.

Interestingly, authors showed an increase of the optic disc rim width, as well as the reversal of the optic disc cupping with normalization of the IOP on the follow-up scans one day after the DRPPT.² Although the number of the subjects ($n = 9$) was small,² this observation is valuable in that it gives hint to the reversibility the ONH morphology related with the short term IOP changes. In clinical practice, we can expect the recovery of the neuroretinal rim structure through prompt normalization of the acute IOP increase. **Furthermore, the question arises about the duration and degree of the IOP rise at which the ONH losses the reversibility.** Future clinical and experimental studies with large subset of subjects are warranted to elucidate this issue.

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2. Wang YX, Jonas JB. Reply: Re: Jiang et al.: Optic nerve head changes after short-term intraocular pressure elevation in acute primary angle-closure suspects (*Ophthalmology* 2015;122:730-7). *Ophthalmology*. 2015;122(12):e73.

Pseudoexfoliation Syndrome



Comment by **Franz Grehn**, Würzburg, Germany

61350 Pseudoexfoliation and cataract surgery: a population-based 30-year follow-up study, Ekström C, Botling Taube A, Acta Ophthalmologica 2015;93(8):774-777

The perspective of this study was to investigate the relation of pseudoexfoliation (PEX) on cataract incidence and cataract surgery. PEX is not only a risk factor for developing open-angle glaucoma and a significant risk factor for complications in cataract surgery, but also may predispose for cataract formation itself. In contrast to previous cross-sectional studies, in this retrospective chart review comprising a total of 1471 eligible individuals from an earlier population survey and other studies of a small town near Uppsala, the ophthalmic findings were followed over several years up to three decades. Taking into account all observation periods, the cohort included a total 15,900 person-years of risk.

PEX is the second strongest predictor for cataract surgery (after lens opacities), accounting for 2,38-fold incidence of cataract surgery in PEX patients

Two-hundred and twenty-four cases were affected by PEX at baseline. Over the years of follow-up, a total of 406 cases were diagnosed with PEX versus 1065 cases had no PEX. By the end of the study, 564 subjects had undergone cataract surgery. The Kaplan-Meier curve shows that the **probability of surviving without cataract surgery is three times higher in non-PEX patients as compared to PEX patients**. Using multivariate analysis the study concludes that PEX is the second strongest predictor for cataract surgery (after lens opacities), accounting for 2,38-fold incidence of cataract surgery in PEX patients. Diabetes mellitus as well as COPD (treatment with steroids) were also risk factors for cataract development. **Oxidative stress is discussed to be a major factor for cataract formation in PEX syndrome**. Although some effects related to smoking and the higher incidence of glaucoma surgery in PEX patients may be considered a confounding factor, the numbers of glaucoma surgery cannot account for the entire difference between PEX and non-PEX cataract surgery.

In summary, this paper clearly demonstrates the higher probability of cataract formation in PEX. Glaucoma specialists are faced with this problem in particular when doing cataract surgery as small pupils, loose zonules and a hard nucleus give rise to potential complications in these patients.

Glaucoma and Systemic Diseases

POAG and Glucose Metabolism Disorders



Comment by **Rupert Bourne**, Cambridge, UK

61623 Association of geroprotective effects of metformin and risk of open-angle glaucoma in persons with diabetes mellitus, Lin HC, Stein JD, Nan B, Childers D, Newman-Casey PA, Thompson DA, Richards JE, JAMA ophthalmology 2015;133:915-923

Growing interest surrounds long-term caloric restriction and the potential benefits this may have in terms of longevity (geroprotection) but also reduction in risk of age-associated diseases, such as cancer, diabetes and cardiovascular disease. Using 'big data', this study sought to investigate whether metformin, a caloric restriction mimetic drug, reduces the incidence of open-angle glaucoma (OAG) among diabetics. True to the definition the data source was 'big', accessing a health claims database of longitudinal data for 40 million patients in a US managed care network.

This raises intriguing questions as to whether metformin reduces OAG risk through mechanisms beyond glycaemic control, such as inflammatory or neurogenesis pathways

The inclusion criteria that required patients to have been enrolled in the pharmaceutical plan of the network for more than two consecutive years with a diagnosis of diabetes and at least one eye examination in that period to exclude those with a pre-existent diagnosis of glaucoma were met by 150,016 patients aged 40 years and older. Patients were followed-up from the date corresponding to their first eye examination until incident OAG was recorded or the last eye examination, whichever came first. Prescriptions filled for diabetic medications were used as a surrogate for medication consumption and survival analysis was conducted to model the effect of metformin exposure on the risk of developing OAG. Aside from some interesting epidemiological findings (3.9% of these diabetics developed incident OAG, and those of African ancestry had a 95% higher risk of OAG than patients of European ancestry), **the analysis revealed that diabetics whose metformin consumption was in the upper quartile had a 25% reduced risk of developing OAG compared with those with no metformin use.** Metformin obviously lowers HbA1C (glycaemic control was incident OAG-protective), yet the risk reduction was still evident even when HbA1C was included in the model. This raises intriguing questions as to whether metformin reduces OAG risk through mechanisms beyond glycaemic control, such as inflammatory or neurogenesis pathways.

POAG and Poor Sleep Quality



Comment by **James Morgan**, Cardiff, UK

61823 Intrinsically photosensitive retinal ganglion cell activity is associated with decreased sleep quality in patients with glaucoma, Graticelli CP, Duque-Chica GL, Roizenblatt M, Moura AL, Nagy BV, Ragot de Melo G, Borba PD, Teixeira SH, Tufik S, Ventura DF, Paranhos A, *Ophthalmology* 2015;122:1139-1148

Graticelli *et al.* report on the changes in the sleep patterns of patients with glaucoma. The background to the potential effect of glaucoma on circadian rhythms has been reported by others. **The study adds to the debate by quantifying the changes in pupillometry as a function of disease.** The pupillometry was tuned to be selective for intrinsically responsive retinal ganglion cells which are thought to be important in entraining the circadian clock.

The principle findings are that sleep disturbances are significant in patients with treated glaucoma compared with age-matched controls. The time to onset of REM sleep as identified a useful benchmark for sleep disturbance. Overall the study contributes to the literature that sleep disturbance is common in patients with glaucoma. **The link to any possible change in photosensitive RGCs is, however, associative and not causative.** The investigators admit to the small size of the study which precludes any robust (multivariate) analysis of the factors that could contribute to sleep disturbance- in particular age, medication, and other concurrent diseases. The thorough assessment of the patient's sleep pattern is commendable but it seems unlikely that this methodology could be applied to large patient cohorts.

Glaucoma can affect patient quality of life in ways that are not captured by conventional measurements of visual performance

The study should remind us that glaucoma can affect patient quality of life in ways that are not captured by conventional measurements of visual performance. It highlights the need for larger studies to dissect the complex interactions of medications/concurrent disease/environment on circadian processes. Knowledge of these factors is important since it could be used to optimize times for the measurement and treatment of those factors by which we gauge disease severity. We also need less demanding surrogate measurements of sleep quality that would fit with a 'big data' approach to this problem.

Medical Treatment

Prostaglandins, Eyelids and Eyelid Muscles



Comment by **Andrew Tatham**, Edinburgh, UK

61498 Prostaglandin eyedrops are associated with decreased thicknesses of eyelid dermis and orbicularis oculi muscle: ultrasonographic findings, Goh AS, Nassiri N, Kohn JC, Rootman DB, Giaconi J, Law SK, Coleman AL, Caprioli J, Goldberg RA, Ophthalmic Plastic and Reconstructive Surgery 2015 July 31; [Epub ahead of print]

This study examined periorbital soft tissue changes due to the use of topical prostaglandin analogues. The authors selected a cohort of **20 patients who had been using prostaglandin analogues in one eye continuously for at least a 12-month period, and for an average of 5½ years.** Fellow eyes were required to have never been treated with a prostaglandin analogue. Thickness of the dermis and orbicularis oculi muscle was assessed using ultrasonography with the operator masked to the eye receiving treatment. The distance from the skin to arcus marginalis on the orbital rim was also measured for upper and lower lids. This distance includes dermis, orbicularis oculi, submuscular areolar and adipose tissue.

Eighty-five percent of patients had thinner periorbital soft tissues in the treated compared to fellow eye with only three patients (15%) not showing any significant difference between eyes. Eyes on prostaglandin analogue therapy had significantly thinner dermis, orbicularis oculi and reduced skin to arcus marginalis distance in upper and lower lids.

The study provides important clues as to why patients using prostaglandin analogues may experience periorbital cosmetic changes such as upper eyelid sulcus deepening

The authors suggest that changes in the skin to arcus marginalis distance may, at least in part, be due to adipocyte atrophy, which could be related to the anti-adipogenic effect of prostaglandin analogues, particularly prostaglandin F2 α . The reason for changes in the dermis and orbicularis oculi is less certain but may be due to an effect on collagen, especially types I, III and IV. However, there are no histological studies to confirm this hypothesis and the subject requires further investigation.

Although the magnitude of soft tissue changes was not related to age, number of glaucoma medications or duration of therapy, these relationships also require further investigation, particularly as the study was limited by a cross-sectional design.

It would be interesting to repeat the study looking for changes over time and explore if the changes are reversible with cessation of therapy. Overall the study provides important clues as to why patients using prostaglandin analogues may experience periorbital cosmetic changes such as upper eyelid sulcus deepening.

Combination Therapy Switch



Comment by **Fotis Topouzis**, Thessaloniki, Greece

61329 Effects of Switching from Timolol to Brimonidine in Prostaglandin Analog and Timolol Combination Therapy, Aihara M, Adachi M, Hamada N, Honda N, Koseki N, Matsuo H, Miyata K, Otani SI, Unoki K, *Journal of Ocular Pharmacology and Therapeutics* 2015; 31: 482-486

Currently prostaglandin analogues (PGAs) are used as first line treatment for lowering intraocular pressure (IOP). Alternative choices exist as second-line drugs in addition to PGA. Additional IOP lowering effects and safety profile of the second-line drugs when used in combination of PGA is of clinical interest.

Aihara *et al.*, conducted a prospective, open-label multi-center study, examining the efficacy and safety of switching from Timolol 0.5% to Brimonidine 0.1% in Japanese patients with glaucoma or ocular hypertension treated with a PGA and Timolol combination. After switching, patients were followed for 12 weeks (visits at 4 and 12 weeks). The main outcome measure was the change in IOP from baseline. Safety evaluations included hyperemia formation, conjunctival follicles, superficial punctate keratopathy (SPK), blood pressure (BP) and heart rate (HR). One hundred and seven patients participated while 103 patients completed the study. **IOP was significantly reduced at 4 and 12 weeks (14.3 ± 2.8 and 14.0 ± 2.8 mmHg, respectively) compared to baseline (15.7 ± 2.7 mmHg) ($p < 0.001$).** However, investigators concluded that switching from Timolol 0.5% to Brimonidine 0.1% may not change the reduction of IOP in the combination use of Timolol 0.5% and a PGA. It is clear that this conclusion does not rely on actual data from the study but on highlighting limitations of the study in discussion and on assumptions arising from those limitations driving the authors' interpretation of the results. Indeed, the open-label design has inherent limitations. In addition, the study included only one arm and one-way switching design. A double-masked two-arm cross-over study design would have been more informative. In addition, there is a well-known tachyphylaxis effect associated with long-term use of Timolol, and the study does not provide any information on the time-length of Timolol use by study participants. Another important limitation is that patients were not washed-out from Timolol and therefore no information on baseline IOP under PGA only is provided. This limits the ability of the study to provide information on the additional IOP of lowering effects of Timolol and Brimonidine when used in combination with a PGA. Also,

interpreting the results, one should keep in mind that this study included Japanese patients with well controlled IOP at baseline (15.7 ± 2.7 mmHg) and therefore generalizability of the results may be limited. Statistically significant differences in SPK, BP and HR were found after switching but they were qualified as not clinically significant. A double-masked, two-arm, cross-over study and with longer follow up under each treatment regimen would be needed to answer the research questions of this study.

Anti-VEGFs for Neovascular Glaucoma



Comment by **Nitin Anand**, Gloucester, UK

61074 Aflibercept for the treatment of neovascular glaucoma, SooHoo JR, Seibold LK, Pantcheva MB, Kahook MY, Clinical and Experimental Ophthalmology 2015;43(9):803-807

Anti-VEGFs have revolutionized the management of anterior segment neovascularization and attendant glaucoma. **The authors investigated the effect of intravitreal aflibercept, the latest anti-VEGF, in four diabetic patients with iris new vessels and open angles (neovascular glaucoma stage 1 and 2).** Aflibercept has several advantages over earlier anti-VEGFs, like bevacuzimab, commonly used for regression of anterior segment neovascularization. It is a more potent inhibitor of VEGF due to its superior binding affinity and pharmacokinetics. It inhibits both VEGF and PlGF, which have been shown to act synergistically in pathological new vessel formation. The disadvantage is the additional cost compared to bevacuzimab.

In the study, patients were to receive one injection at time of diagnosis, at four and eight weeks and then every eight weeks thereafter until 52 weeks. One patient had three aflibercept injections, before refusing further intervention. **Iris new vessels regressed in all four cases. No patient required additional intervention and IOP remained well-controlled.**

As the authors have pointed out, it was an open-label study with no controls. It is possible that the neovascular process may have been arrested with better control of diabetes alone. As well, the optimum dosage schedule remains unclear. Nevertheless, they have pushed the door open for intravitreal aflibercept to be an alternative for the treatment of NVG.

Prolonged Drug Delivery



Comment by **Eytan Blumenthal**, Jerusalem, Israel

61390 Dual drug delivery from vitamin E loaded contact lenses for glaucoma therapy, Hsu KH, Carbia BE, Plummer C, Chauhan A, *European Journal of Pharmaceutics and Biopharmaceutics* 2015;94:312-321

Compliance and side-effects are two notorious drawbacks of medical therapy for glaucoma. 'Moving the patient out of the loop' in the sense that drug delivery will not depend on a periodic action performed by the patient is high on our wish-list for improving glaucoma care. Various approaches have been suggested and tried, including inserts and intraocular slow-release devices.

Hsu *et al.* present a study in which two commonly used drugs, **timolol and dorzolamide, often prescribed in combination, were simultaneously loaded onto a contact lens that was pre-loaded with vitamin E.**

The presence of vitamin E within the contact lens serves to dramatically increase the duration of drug release. The desired decrease in the drug transport rate is achieved by an increase in the diffusion path length in the lens matrix. While drug-soaked contact lenses will release the medication for a period of up to a few hours, the incorporation of vitamin E increased this active period to two days. Vitamin E in this case serves as a diffusion barrier while retaining transparency. Incorporation of vitamin E into the contact lens increased the release duration 35- and 14-fold for timolol and dorzolamide, respectively. Of note, and as yet unexplained, when both drugs were soaked in the same lens, the release duration further increased 1.7- and 1.2-fold. This phenomenon is speculated to be perhaps secondary to a timolol-dorzolamide drug interaction within the contact lens.

The presence of vitamin E within the contact lens serves to dramatically increase the duration of drug release

The approach presented in this study removes the burden of drop administration, for the duration that the contact lens is in the eye, but not the compliance needed to place and replace the contact lens periodically (in our case, every two days). In this study, commercially available (standard) soft contact lenses were 'loaded' with IOP-lowering drugs.

These Vitamin E-timolol-dorzolamide pre-loaded lenses were studied on Beagle dogs harboring primary open-angle glaucoma. In comparison to the control group that received standard drop therapy, the group receiving the contact lens therapy enjoyed a stable IOP reduction that lasted as long as a week and more from a single contact lens.

Surgical Treatment

What to do when Drainage Devices Fail?



Comment by **Steven Gedde**, Miami, FL, USA

61061 Failed glaucoma drainage implant: long-term outcomes of a second glaucoma drainage device versus cyclophotocoagulation, Schaefer JL, Levine MA, Martorana G, Koenigsman H, Smith MF, Sherwood MB, British Journal of Ophthalmology 2015; [Epub ahead of print]

Glaucoma drainage devices (GDDs) are being used with increasing frequency in the surgical treatment of glaucoma. Opinions differ regarding the preferred approach when intraocular pressure (IOP) remains uncontrolled after GDD placement despite reinstitution of medical therapy. Needling the bleb over the end plate, capsule excision, cyclophotocoagulation (CPC), and implantation of a second GDD have all been advocated in the setting of primary GDD failure.

Schaefer and colleagues retrospectively evaluated the long-term outcomes of 32 eyes that underwent CPC and 15 eyes that had implantation of a second GDD after failure of an initial GDD. **Additional surgical intervention for glaucoma was required in 11 (34%) eyes in the CPC group and nine (60%) eyes in the GDD group.** The majority of CPC failures occurred during the first year of follow-up, while the majority of second GDD failures were observed after five years. The mean follow-up after the second procedure was 63 ± 65.8 months in the CPC group and 132 ± 91.8 months in the GDD group.

A randomized clinical trial is needed to definitively answer the question of whether CPC or placement of a second GDD is the preferred treatment when an initial GDD does not provide adequate IOP control

Although no significant differences were noted in the baseline characteristics between the CPC and GDD groups, there may have been other factors that directed the surgeon toward one treatment or the other. Visual acuity, IOP, medical therapy, and failure data are presented at last follow-up. However, this information is not meaningful, given the marked difference in duration of follow-up between the two study groups. Kaplan-Meier survival analysis and outcomes data at one year are also provided, but no statistical comparisons are made between the CPC and GDD groups.

The authors are to be congratulated for adding important information about the management of patients who fail primary GDD implantation. As suggested, a randomized clinical trial is needed to definitively answer the question of whether CPC or placement of a second GDD is the preferred treatment when an initial GDD does not provide adequate IOP control.

Drainage Devices in Pediatric Glaucoma



Comment by **Jose-Maria Martinez de la Casa**, Madrid, Spain

61370 Valved glaucoma drainage devices in pediatric glaucoma: retrospective long-term outcomes, Chen A, Yu F, Law SK, Giaconi JA, Coleman AL, Caprioli J, JAMA ophthalmology 2015;133(9):1030-1035

In this paper, Chen *et al.* present a retrospective study about 119 eyes of 89 patients with pediatric glaucoma who underwent Ahmed glaucoma valve (AGV) implantation. Mean age at time of implantation was 6.8 ± 5.7 years and mean follow-up was 6.1 ± 3.3 years (range 1 to 14.2 years).

Mean IOP decrease was 13.0 mmHg (95%CI, 8.8 to 17.3 mmHg) at five years postoperatively without significant differences in hypotensive medications requirements compared to baseline. The success rates for all eyes were 85.7% (95% CI, 79.7%- 92.2%) at one year and 36.8% (95%CI, 26.8%-50.4%) at ten years. The success rate at five years was 41.8% (95%CI, 26.5%-66.0%) for eyes with primary glaucoma, 75.0% (95% CI, 57.7%-97.5%) for uveitic eyes, and 53.9% (95% CI, 41.8%-69.4%) for eyes with other secondary glaucoma. There were no significant differences between groups. Surprisingly, unlike previous studies,^{1,2} **five years survival rate was significantly higher with polypropylene (S-2) implants than with silicone ones (FP-7) 66.9% vs 41.2% ($p < 0.001$).**

Risk factor analysis showed that older age (risk ratio = 0.95; 95%CI, 0.90-0.99; $P = .02$), uveitic glaucoma (risk ratio = 0.34; 95% CI, 0.14-0.86; $P = .02$), and polypropylene AGVs (risk ratio = 0.39; 95%CI, 0.23-0.67; $P = .001$) were associated with higher success rates. Tube revision (21.8%), cataract progression requiring cataract surgery (4.2%) and strabismus surgery (2.5%) were the most frequent complications during the follow up. Complications were not associated with diagnosis or AGV model. Thirty six eyes (30.2%) received a second AGV. The success rate for this second implant was 52.8% (95%CI, 37.0%-75.3%) at 5years.

In summary, with the limitations of a retrospective study, the authors have collected information on an important case series of pediatric glaucoma that will help in the management of this complex pathology

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Drainage Devices and Prolonged Drug Delivery



Comment by **Ingeborg Stalmans**, Leuven, Belgium

61681 Effect of two novel sustained-release drug delivery systems on bleb fibrosis: an in vivo glaucoma drainage device study in a rabbit model, Schoenberg ED, Blake DA, Swann FB, Parlin AW, Zurakowski D, Margo CE, Ponnusamy T, John VT, Ayyala RS, Translational Vision Science & Technology 2015;4(3):4

The authors' research focuses on the development of drug-eluting systems to be used in conjunction with glaucoma surgery. They **designed and evaluated two polymer systems to be attached to an Ahmed glaucoma valve**: on the one hand a non-biodegradable poly(2-hydroxyethyl methacrylate) (P[HEMA]) system with mitomycin C (MMC), and on the other hand a biodegradable poly(lactic-co-glycolic acid) (PLGA) system with 5-fluorouracil (5-FU) with and without a film releasing MMC.

5-FU did not seem to significantly reduce bleb wall thickness at either tested concentration

Preclinical testing in rabbits revealed both MMC-eluting systems to be effective in reducing bleb wall thickness (although without a difference in histological fibrosis), without significant clinical or histological signs of toxicity over a three-month postoperative period.

Interestingly, the PLGA system coated with an MMC film allowed a ten-fold reduction in MMC concentration compared with the P[HEMA] system. However, the MMC delivery period was also five to ten times shorter in the PLGA device (one to two days compared to ten days in the P[HEMA] system), which makes it difficult to interpret the impact on safety between the two devices. The safety data during the three-month follow-up period were favorable, but this time-frame is not sufficient to understand long-term side effects of MMC.

Of note, 5-FU did not seem to significantly reduce bleb wall thickness at either tested concentration, which is consistent with the published literature indicating that 5-FU is significantly less effective than MMC as an adjunctive to glaucoma surgery.

In conclusion, the authors are to be congratulated for their efforts to improve efficacy and safety of glaucoma surgery. Further preclinical and clinical studies will be required allow to further explore this promising path.

Mitomycin



Comment by **Yvonne Buys**, Toronto, Canada

61164 Evaluating the long-term efficacy of short-duration 0.1mg/ml and 0.2mg/ml MMC in primary trabeculectomy for primary adult glaucoma, Sihota R, Angmo D, Chandra A, Gupta V, Sharma A, Pandey RM, Graefe's Archive for Clinical and Experimental Ophthalmology 2015;253:1153-1159

Success rates of trabeculectomy have improved with the introduction of mitomycin C (MMC). However, increased concentration and/or duration of MMC exposure is also related to increased complications, specifically vision threatening complications such as hypotony, bleb leaks and infection. Titrating MMC exposure to find a balance between success and complications is required. Sihota *et al.* report on the **two-year results of a prospective randomized study of 50 subjects with primary open- or closed-angle glaucoma without a history of previous eye surgery who were randomized to trabeculectomy with one minute of 0.1 or 0.2 mg/ml MMC**. They reported **no difference in success or complications however the 0.2 mg/ml MMC group had larger blebs with more transparent/thin areas**.

Lower concentrations and short MMC exposure may not impact efficacy but could minimize complications and underscores the importance of monitoring one's surgical results over the long term to suggest modifications to current surgical technique

Although these results suggest low-concentration, short-exposure MMC is equally effective to higher concentrations and longer exposure, the study fails to provide important details including the location of MMC application and rates of suture lysis. The definition of success changes from the study design (6-15 mmHg) to discussion (≤ 15 mmHg). Figure 1 seems to have a low outlier in the 0.1 mg/ml group which might change the complete success rate from 92% to 88% in addition the complete success rate of the 0.2 mg/ml group was reported as 88% in the results and 91.7% in the discussion. Surprising is the virtually 100% complete and qualified success rates at two years (the one failure, IOP 16 mmHg on two medications, experienced trauma on post-op day two) and zero complications. The authors acknowledge this and attribute it to the small sample size.

Surgical studies can be difficult to translate into individual practice given varying techniques. In addition filtration surgery results are significantly impacted by post-operative care. It is unlikely that a 'one-size-fits-all' approach can be applied to MMC use. However, this study highlights

that lower concentrations and short MMC exposure may not impact efficacy but could minimize complications and underscores the importance of monitoring one's surgical results over the long term to suggest modifications to current surgical technique.

Refractory Glaucoma



Comment by **Peter Shah**, Birmingham, UK

61117 High-intensity focused ultrasound treatment in refractory glaucoma patients: results at 1 year of prospective clinical study, Melamed S, Goldenfeld M, Cotlear D, Skaat A, Moroz I, European Journal of Ophthalmology 2015;25(6):483-489

The current clinical standard for destruction of the ciliary body in refractory glaucoma is trans-scleral diode laser cyclophotocoagulation. Concerns exist, however, that due to the relatively non-selective nature of laser absorption there is potential for adjacent collateral tissue damage to the iris and choroid.

Melamed *et al.* report on the safety and efficacy of **ultrasonic** cyclocoagulation using high-intensity focused ultrasound (**HIFU**) delivered by an annular device containing six piezoceramic transducers. This was a prospective interventional non-comparative study of 20 eyes with refractory glaucoma using intraocular pressure (IOP) reduction as the main primary outcome measure. **Surgical success was achieved in 65% of eyes, with a mean post-operative IOP of 22.5 mmHg reduced from a pre-operative mean of 36.4 mmHg.**

The results are comparable with published series of diode laser cyclophotocoagulation, however, there is an important potential source of bias in the HIFU data. The refractory glaucoma cases in the HIFU study had the following glaucoma etiologies: POAG (65%), PXF (20%), Pigmentary (5%) and other (10%). The study did not have many eyes with neovascular, developmental or post-surgical glaucoma (e.g., post-keratoplasty).

The authors report **no major complications and no cases of hypotony, but detailed analysis reveals corneal edema in 20% and opacification in 5% of eyes. At one year post-treatment visual acuities were the same / improved in 65%, and reduced by one line or more in 35%.** The corneal complications reported need further evaluation as many cases of unselected refractory glaucoma have corneal co-pathology.

One of three standard ring treatment diameters (11, 12 or 13mm) could be used, but the approach to regional variations in ciliary body (CB) anatomy within an eye (e.g., **variable recession** of the CB in post-surgical cases) was not discussed.

This is a well-written and interesting report of 20 treated eyes, but further work is needed to establish the role of HIFU cyclocoagulation in more complex refractory glaucoma.

Phaco-and-Stent



Comment by **Malik Kahook**, Denver, CO, USA

61132 A randomized trial of a Schlemm's canal microstent with phacoemulsification for reducing intraocular pressure in open-angle glaucoma, Pfeiffer N, Garcia-Feijoo J, Martinez-de-la-Casa JM, Larrosa JM, Fea A, Lemij H, Gandolfi S, Schwenn O, Lorenz K, Samuelson TW, *Ophthalmology* 2015;122:1283-1293

Micro-incisional glaucoma surgery (MIGS) has become a viable option for treating mild to moderate glaucoma with an attractive risk-benefit profile for many patients. MIGS options that are widely available for patient care include procedures that do not require device implantation, such as endocyclophotocoagulation (Beaver Visitec) and Trabectome (Neomedix), as well as implant-based procedures such as the iStent (Glaukos Laguna, Hills CA). Another implantable option is the Hydrus Microstent (Ivantis, Inc, Irvine, CA). The microstent is implanted ab interno through a clear corneal incision into the canal of Schlemm allowing aqueous humor outflow to bypass the trabecular meshwork while dilating the canal over three clock hours. A recent **prospective multi-center trial was completed to assess the safety and efficacy of the Hydrus Microstent combined with cataract surgery (CS) for reducing intraocular pressure (IOP) in eyes with open-angle glaucoma (OAG)**. A total of 100 eyes from 100 patients with IOP < 24 mmHg and four or fewer glaucoma medications were enrolled in the study and **randomized 1:1 to either CS with Hydrus or CS alone. All patients had a washed-out diurnal IOP (DIOP) of 21 to 36 mmHg. The proportion of patients with a 20% reduction in washed-out DIOP was 80% in the Hydrus plus CS group at 24 months compared with 46% in the CS alone group (P = 0.0008). Washed-out mean DIOP in the Hydrus plus CS group was 16.9 ± 3.3 mmHg at 24 months compared with 19.2 ± 4.7 mmHg in the CS alone group (P = 0.0093)**. Seventy-three percent in the Hydrus-plus CS group vs 38% in the CS-only group were off glaucoma medications at 24 months (P = 0.0008). Adverse events were similar between groups. This study shows the potential for Hydrus to significantly and safely lower IOP in patients with OAG who also require cataract extraction. Future studies that compare efficacy and safety of Hydrus versus existing MIGS devices, such as the iStent, will help physicians and patients select the most appropriate therapy for optimal results.

References

1. Pircher M, Hitzenberger CK, Schmidt-Erfurth U. Polarization sensitive optical coherence tomography in the human eye. *Prog Retin Eye Res* 2011;30(6):431-451.
2. Vermeer KA, van der Schoot J, Lemij HG, de Boer JF. RPE-normalized RNFL attenuation coefficient maps derived from volumetric OCT imaging for glaucoma assessment. *Invest Ophthalmol Vis Sci* 2012;53(10):6102-6108.

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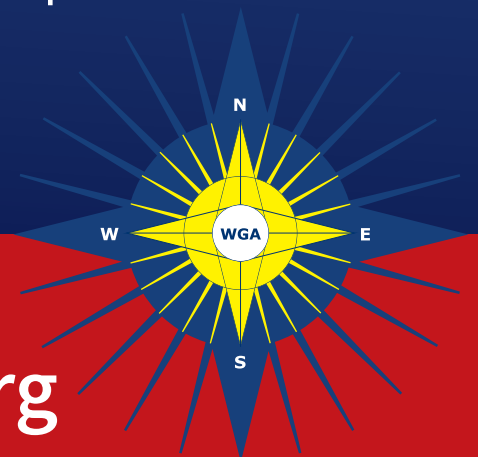
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- ★ Glaucoma can affect patient quality of life in ways that are not captured by conventional measurements of visual performance
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